REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-17, 20-21, and 27-36 presently appear in this application, with claims 2-5, 15 and 16 withdrawn, and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 22-26 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The examiner's helpful suggestions for composition claims are adopted thereby obviating this rejection. Applicants' point out for the examiner's attention that composition claim 33 is directed to a composition containing a peptide in an amount effective to inhibit growth of the protozoan. *Leishmania mexicana* in Example 12 on page 53 of the specification is a protozoan that is inhibited by the presently claimed peptide. Claim 31 is added to recite inhibition of viral activity and claim 29 is added to recite inhibition of cancer cell proliferation.

Claims 14 and 17 contain underlining or brackets that are apparently intended to appear in the printed patent or are

properly part of the claimed material. The examiner suggests that a new system be adopted for underlining and bracketing. It is respectfully pointed out that the rules requiring amendments/changes to the claims by underlining and bracketing have changed. Brackets and underlines are no longer used for claim amendments and it is submitted that there would be no confusion as a result of the presence of brackets and underlines in a printed patent at this point in time.

Claims 1, 6-14, and 17-26 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is obviated by the amendment to the claims. The examiner's suggestion for the claim language in claim 19 has been adopted in new claim 37.

Claims 1, 2, and 7-11 have been rejected under 35 U.S.C. 102(e) as being anticipated by Maloy, U.S. Patent No. 5,792,831. The examiner states that the claims are anticipated because Maloy teaches cytolytic peptides containing D-amino acids. This rejection is respectfully traversed.

Maloy teaches D-amino acid analogues of naturally-occurring magainin peptides. Claim 1 (B) recites for a cytolytic peptide comprising both L-amino acid residues and D-amino acid residues, where if the D-amino acid residues were only present as L-amino acid residues, then the cytolytic peptide having only L-amino acid residues is not naturally-occurring, i.e., not found

in nature. This is certainly not the case for the D-amino acid analogues of Maloy. If the residues present in the D-form are only present in the L-form in Maloys' peptides, then those peptides would be naturally-occurring magainin peptides. With regard to claim 1 (A), (C) or (D), and claims directed to a mixture, Maloy does not disclose anything about cyclic peptides, a complex or a mixture of peptides, or random copolymers. Accordingly, Maloy cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claim 1 has been rejected under 35 U.S.C. 102(b) as being anticipated by Shai, *J. Biol. Chem* 271:7305 (1996). The examiner states that the claim is anticipated because Shai teaches on page 7308, column 1, first paragraph, that the peptide designated (D)$P^{7}L^{18}L^{19}$ is antibacterial but non-hemolytic. This rejection is respectfully traversed.

The (D)$P^{7}L^{18}L^{19}$ pardaxin derivative taught in the applied Shai reference is the same as peptide 16 presented on page 26 and in Table 1 (pages 29-30) of the specification. This peptide does not fall within the scope of the claims because the peptide "with the corresponding amino acid sequence comprising only L-amino acid sequence comprising only L-amino acid residues" <u>is</u> found in nature, contrary to what is recited in claim 1 (B). Furthermore,

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the present specification corrects the applicants' own previous work in the applied Shai reference by showing in Table 1 that peptide 16 is indeed hemolytic. Accordingly, Shai cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claim 1 has been rejected under 35 U.S.C. 102(b) as being anticipated by Oren, *J. Biol. Chem* 272:14643 (1997). The examiner states that the claim is anticipated because Oren teaches a few peptides which are antibacterial, but only minimally hemolytic. This rejection is respectfully traversed.

The publication date of the applied Oren reference is June 1997. Accordingly, Oren is not available as a prior art reference because the present application is entitled to the benefit of priority of the February 20, 1997, filing date of PCT International application PCT/IL97/00066 designating the U.S.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

In view of the above, the present claims comply with 35 U.S.C. 112 and define patentable subject matter warranting their

allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1, 6-8, 10, 14-17, and 19-20 have been amended as follows:

1(Amended). A non-hemolytic cytolytic ~~agent selected from a peptide, a complex of bundled peptides, a mixture of peptides or a random peptide copolymer, said agent~~peptide having a selective cytolytic activity manifested in that it has a cytolytic activity on pathogenic cells, said pathogenic cells being cells which are non-naturally occurring within the body consisting of microbial pathogenic organisms and malignant cells; and it is non-hemolytic, namely it has no cytolytic effect on red blood cells or has a cytolytic effect on red blood cells at concentrations which are substantially higher than that in which it manifests said cytolytic activity, said non-hemolytic cytolytic ~~agent~~ peptide being selected from the group consisting of:

(~~1~~A) a cyclic derivative of a peptide having a net positive charge which is greater than +1, and comprising both L-amino acid residues and D-amino acid residues, or comprising one or both of L-amino acid residues and D-amino acid residues, and comprising an α-helix breaker moiety;

(~~2~~B) a peptide comprising both L-amino acid residues and D-amino acid residues, having a net positive charge which is greater than +1, and having a sequence of amino acids such that a

corresponding amino acid sequence comprising only L-amino acid residues is not found in nature, and cyclic derivatives thereof;

(~~3~~C) a complex consisting of a plurality of 2 or more non-hemolytic cytolytic peptides, each peptide having a net positive charge which is greater than +1, and comprising both L-amino acid residues and D-amino acid residues, or comprising one or both of L-amino acid residues and D-amino acid residues and comprising an α-helix breaker moiety, or cyclic derivatives of the foregoing, said peptides being ~~bundled~~ linked together by the use of a linker molecule covalently bound to each of the peptides;

~~(4) a mixture consisting of a plurality of 2 or more non-hemolytic cytolytic peptides, each peptide having a net positive charge which is greater than +1, and comprising both L-amino acid residues and D-amino acid residues, or comprising one or both of L-amino acid residues and D-amino acid residues and comprising an α-helix breaker moiety, or cyclic derivatives of the foregoing;~~ and

(~~5~~D) a random copolymer consisting of ~~different ratios~~ a ratio of a hydrophobic, a positively charged and a D-amino acid.

6(Twice-amended). The cyclic peptide according to claim ~~5~~1 selected from the cyclic pardaxin-derived peptides

herein designated peptides **86-88** (SEQ ID NOs: 86-88, respectively), of the sequence:

86. Cyclic K^1[D]P^7 $L^{18}L^{19}$ [1-22]-par of the sequence:

Cys-Lys-Gly-Phe-Phe-Ala-Leu-Ile-**Pro**-Lys-Ile-Ile-Ser-
Ser-Pro-Leu-Phe-Lys-Thr-**Leu-Leu**-Ser-Ala-Val-Cys

87. Cyclic K^1 K^2[D]P^7 $L^{18}L^{19}$ [1-22]-par of the sequence:

Cys-Lys-Lys-Gly-Phe-Phe-Ala-Leu-Ile-**Pro**-Lys-Ile-Ile-Ser-
Ser-Pro-Leu-Phe-Lys-Thr-Leu-Leu-Ser-Ala-Val-Cys

88. Cyclic K^1 K^2K^3 [D]P^7 $L^{18}L^{19}$ [1-22]-par of the sequence:

Cys-Lys-Lys-Lys-Gly-Phe-Phe-Ala-Leu-Ile-**Pro**-Lys-Ile-Ile-
Ser-Ser-Pro-Leu-Phe-Lys-Thr-**Leu-Leu**-Ser-Ala-Val-Cys

7(Amended). The peptide according to claim 1 (~~2~~B), comprising both L-amino acid residues and D-amino acid residues and having a sequence of amino acids such that a corresponding amino acid sequence comprising only L-amino acid residues is not found in nature.

8(Amended). The peptide according to claim 7, having the following characteristics:

(a) it is a non-natural synthetic peptide composed of ~~varying ratios~~ a ratio of at least one hydrophobic amino acid and at least one positively charged amino acid, and in which sequence at least one of the amino acid residues is a D-amino acid;
(b) the peptide has a net positive charge which is greater than +1; and
(c) the ratio of hydrophobic to positively charged amino acids is such that the peptide is cytolytic to pathogenic cells but does not cause cytolysis of red blood cells.

10(Amended). The peptide according to claim 9, wherein the net positive charge greater than +1 is due to the amino acid composition or to the addition of positively charged chemical groups, or which hydrophobicity ~~may be~~ is decreased by the addition of polar amino acids ~~such as~~ selected from the group consisting of serine, threonine, methionine, asparagine, glutamine and cysteine.

14(Thrice-Amended). The cyclic derivative of a non-natural synthetic peptide according to claim 7, selected from the peptides herein designated 92-95 (SEQ ID NOS: 92-95, respectively), of the sequence:

92. Cyclic Cys Lys Leu **Leu** **Leu** Lys Leu Leu **Leu** Lys Leu Leu Lys Cys

93. Cyclic Cys Lys Leu **Leu** **Leu** Lys Leu Lys **Leu** Lys **Leu** Lys Cys

94. HN - Lys Leu **Leu** **Leu** Lys Leu Leu **Leu** Lys **Leu** Leu Lys - CO

95. HN - Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys - CO

15(Twice-Amended). A complex of ~~bundled~~ peptides according to claim 1(~~3~~C) consisting of a plurality of 2 or more non-hemolytic cytolytic peptides according to claim 1, said peptides being ~~bundled~~ linked together through a linker molecule covalently bound to each of the peptides.

16(Amended). The complex according to claim 15, ~~wherein the bundle~~ which is composed of 2 or more, ~~preferably 5,~~ molecules of the same peptide or of different peptides, and the linker is a peptide ~~according to any one of the preceding claims~~ or a commonly used linker.

17(Twice-Amended). The complex according to claim ~~16~~ ~~selected from~~ 1, wherein the ~~bundled~~ linked Lys/Leu diastereomers herein designated 96 and 97 are covalently linked together through a linker molecule:

96. $([D]\text{-}L^{3,4,8,10}\text{-}K_4L_8C)_5\ [D]\text{-}L^{3,4,8,10}\text{-}K_4L_8$ of the sequence:

(Lys-Leu-**Leu-Leu**-Lys-Leu-Leu-**Leu**-Lys-**Leu**-Leu-Lys-Cys-NH_2)$_5$ Lys-Leu-**Leu**-**Leu**-Lys-Leu-Leu-**Leu**-Lys-**Leu**-Leu-Lys-NH_2 (SEQ ID NOs: 96 and 23)

97. ([D]-$L^{3,4,8,10}$-K_5L_7C)$_5$ [D]-$L^{3,4,8,10}$-K_4L_9 of the sequence: (Lys-Leu-**Leu-Leu**-Lys-Leu-Lys-**Leu**-Lys-**Leu**-Leu-Lys-Cys-NH_2)$_5$ Lys-Leu-**Leu-Leu**-Lys-Leu-Leu-**Leu**-Lys-**Leu**-Leu-Lys-NH_2 (SEQ ID NOs: 97 and 24).

19(Amended). The mixture according to claim ~~18~~ 36, comprising a mixture of Lys/Leu 12-mer peptide diastereomers.

20(Amended). The non-hemolytic cytolytic random copolymer according to claim 1(~~5~~D), consisting of different ratios of a hydrophobic, a positively charged and a D-amino acid~~,~~.